REMARKS

Claims 11-42, 63, 65-86, 88, 89, 94-101 and 106-108 are pending in this application. Claims 11-42, 65-70, 73, 76-82, 85, 88 and 89 have been withdrawn from consideration deemed non-elected subject matter. Claims 63, 71, 72, 74, 75, 83, 84, 86, 94-101 and 106-108 that read on species "Amb a1" as the specific antigen and "AACGTTCG" as a specific ISS are being acted upon by the Examiner. Claims 63, 71, 72, 74, 75, 83, 84, 86, 94-101 and 106-108 were variously rejected under 35 U.S.C. § 112, first paragraph. Claims 71, 72, 83 and 84 were rejected under 35 U.S.C. § 112, second paragraph.

By this amendment, claim 75 has been amended without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments can be found, *inter alia*, throughout the specification, for example at page 23, lines 14-15. As discussed herein, the amendment is made to better place the application in condition for allowance by amending to the exact language from the specification in view of the new matter rejection. Thus, Applicants respectfully submit that the amendment is does not raise new issues and respectfully request entry of this amendment.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and canceled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §112, first paragraph

Claims 63, 71, 72, 74, 75, 83, 84, 86, 94-101 and 106-108 were variously rejected under 35 U.S.C. §112, first paragraph. Applicants respectfully traverse these grounds for rejection.

The Examiner notes on page 2 that the Office Action is directed to the claims as they read on the specific antigen species "Amb a1" and the specific ISS species "AACGTTCG." Accordingly, Applicants' remarks will be directed primarily to the specific rejections raised in the Office Action. By directing remarks specifically to the elected species, Applicants do not acquiesce to any of the Office's rejections or surrender the broader scope of the claims with regard to antigen and ISS genera. Applicants understand that, upon allowance of the elected species, the Examiner will continue examination of other species within the claimed genera. Applicants also understand that, upon allowance of a generic claim, the remainder of the species be included as permitted by 37 C.F.R. § 1.141(a).

Enablement

Claims 63, 71, 72, 74, 75, 83, 84, 86, 94-101 and 106-108 were rejected for allegedly not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. Applicants respectfully traverse this rejection.

The court in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), found that the enablement requirement was satisfied by a "disclosure [that] provides considerable direction and guidance on how to practice [the] invention and presents working examples," in view of the fact that "[t]here was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." *Id.* at 740. "Since one embodiment is ... disclosed in the specification, along with the general manner in which its current range was ascertained, ... other permutations of the invention could be practiced by those skilled in the art

without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d. 788, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).

In order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); M.P.E.P. §2164.04.

The Examiner states that the specification is enabling for a population of conjugate molecules comprising a ragweed pollen allergen, such as Amb a1, and an immunostimulatory sequence (ISS) consisting of a sequence selected from the group consisting of SEQ ID NO:1-8. The Examiner also states that the specification does not reasonably provide enablement for any ISS comprising the sequence 5'-CG-3' or for any ISS comprising the sequence 5'-purine, purine, C, G, pyrimidine, pyrimidine, C, G-3'. Office Action, page 3. The Examiner then concludes that "it would require undue experimentation even for one skilled in the art to practice the claimed invention." Office Action, page 5.

The Examiner's concerns essentially relate to the effective "scope" of enablement and whether the specification adequately supports and enables the ISS as claimed to one of skill in the art. Base on the following, Applicants respectfully submit that the Examiner's concerns regarding enablement are misplaced and unnecessary.

The invention is based on the discovery that the ratio of ISS to antigen in a conjugate molecule can alter the immunostimulatory and biological activities of the conjugate molecule. For example, as the ratio of ISS to antigen increases for a population of conjugate molecules, the allergenicity of the molecules decreases, as does the ability of the molecules to stimulate antibody production. Thus, the claimed invention is directed to populations of ISS-antigen conjugate molecules with varying activities. Antigens for use in the claimed invention are well known in the art. Polynucleotides greater than 6 and less than about 200 nucleotides in length comprising an ISS, wherein the ISS comprising a CG dinucleotide, are also well known in the art. The invention lies in

the unique combination and resultant activity of the ISS-antigen conjugate molecules prepared according to the instant specification.

Oligonucleotides comprising ISS for use in the present invention are described in the specification and well known in the art. Contrary to the Examiner's assertion at page 6 of the Office Action that only eight specific immunostimulatory sequences are disclosed in the specification, pages 36-43 of the specification provide over 75 examples of ISS for use in the invention, as well as methods for making additional ISS-containing polynucleotides. At pages 66-69, the specification provides methods by which the skilled artisan can assess the activity of any ISS-containing polynucleotide. Applicants also submit that ISS comprising a CG dinucleotide were well known in the art at the time the application was filed and that the relative level of skill in the art is high. A review of the many references regarding CG-containing immunostimulatory sequences cited in the specification and submitted to the Office clearly shows that a CG dinucleotide is a necessary element of the claimed category of immunostimulatory sequences. Such extensive disclosure provides adequate guidance such that a skilled artisan would be able to practice the invention without undue experimentation.

The Examiner relies on the references of Van Uden, Segal and Yamada[1] to support the lack of enablement rejection. Van Uden describes immunostimulatory DNA and it application to allergic disease. As noted by the Examiner, on page 903 Van Uden states that the precise "DNA sequence structure required for immune stimulation ... is only partially understood." However, Van Uden then presents 36 CG-containing sequences as "potent immunostimulatory DNA sequences" in Table 1 and goes on to state that the dinucleotide 5'-CG-3' is generally required for immunostimulatory activity. See, for example, Van Uden page 904. All of the CG-containing sequences taught in Van Uden had immunostimulatory activity. Taken in its entirety, Van Uden

[1] Van Uden et al. (1999, *J. Allergy Clin. Immunol.* 104:902-910, "Van Uden"), Segal et al. (2000, *J. Immunol.* 164:5683-5688, "Segal"), Yamada et al. (2002, *J. Immunol.* 169:5590-5594, "Yamada"), all cited in Office Action.

teaches that a CG dinucleotide is a critical element for immunostimulatory activity of the oligonucleotide.

Throughout, Segal refers to "CpG-containing oligonucleotides" as immunostimulatory and the only requirement taught for the immunostimulatory activity of an oligonucleotide by Segal is the presence of a CG dinucleotide. Thus, Segal teaches immunostimulatory activity of oligonucleotides containing a CG dinucleotide and presents nothing that conflicts with this. A skilled artisan reading Segal would not question the structural requirement for an immunostimulatory oligonucleotide. Segal does nothing to support the alleged lack of enablement of the claimed invention with regard to requirements for the claimed oligonucleotide structure.

Applicants respectfully point out that Yamada describes features of DNA sequences which suppress immune activation by immunostimulatory DNA, not features of the immunostimulatory DNA itself. In fact, Yamada is focused on the description of DNA sequences with suppressive activity and provides nothing to support the alleged lack of enablement of the instant invention.

The Examiner further states that the term "comprising" expands the ISS "to include additional undisclosed nucleotides at either or both ends so long the nucleotide sequence has a 5' cytosine and a 3' guanine."[2] Office Action, page 4. Applicants respectfully submit that the inclusion of the term "comprising" with regard to the oligonucleotide in the claims leaves the claims fully enabled by the specification. As discussed, immunostimulatory oligonucleotides of varying lengths are well-known in the art. Van Uden, for example, describes immune stimulation associated with oligonucleotides and associated with gene vaccination from immunostimulatory sequences within a plasmid backbone. Thus, immunostimulatory sequences are known to be active with a variety of flanking sequences and a variety of lengths.

[2] As discussed herein in the section on the indefiniteness rejection, interpretation of the ISS as requiring a terminal 5' cytosine and a terminal 3' guanine is incorrect. Rather, the ISS of the claimed invention requires a CG dinucleotide within the sequence.

Applicants respectfully submit that none of these references, when taken in its entirety, support the alleged state of unpredictability with regard to the claimed invention and thus, do not provide acceptable documentation or sound scientific reasoning to support any doubt of the teachings of the specification. See, for example, *In re Marzocchi*, 439 F2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). Unless such documentation and/or scientific reasoning are adduced, the statements made in the specification are to be taken at face value. Thus, Applicants respectfully submit that a *prima facie* case for lack of enablement has not been established and that the claimed invention is enabled by the specification.

In addressing Applicants' remark regarding the Office's issuance of claims directed to administering ISS-containing polynucleotides comprising a CG dinucleotide, the Examiner noted that every application is examined on its own merits. Applicants submit, however, that, just as such patents inform the skilled artisan, such patents are also appropriate to inform the Examiner as to the state of the art with regard to the claimed subject matter.

According to the Office, claims are not rejected as broader than the enabling disclosure under 35 U.S.C. §112 for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art; the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider obvious. M.P.E.P. §2164.08. The court has stated that "Enablement is not precluded by the necessity for some experimentation such as routine screening ...". *In re Wands*, 858 F2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Applicants respectfully submit that varying the nucleic acid sequence of oligonucleotides and testing the oligonucleotides for immunostimulatory activity are well within the bounds of routine experimentation by one of skill in the art.

Fulfillment of the enablement requirement does not require that every embodiment of the invention be predictable. Rather, unpredictability is permitted, the level of unpredictability permitted depending on the level of guidance provided by the specification and the knowledge in the

art. Applicants respectfully note that the test for enablement is not whether a certain amount of experimentation is required to practice an invention, but rather whether the amount of experimentation is "undue." *In re Wands, Supra,* (Fed. Cir. 1988). Applicants respectfully submit that the specification has provided a reasonable amount of guidance to the skilled artisan with respect to CG-containing immunostimulatory oligonucleotides as claimed and that the skilled artisan would be able to extend the teachings of the specification and the art to the methods as claimed.

Thus, Applicants respectfully submit that a *prima facie* case of lack of enablement has not been established. Accordingly, the pending claims are in compliance with the enablement requirements.

Written Description

Claims 63, 71, 72, 74, 75, 83, 84, 86, 94-101 and 106-108 were rejected as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

The Examiner asserts that the specification does not reasonably provide a written description of any ISS comprising the sequence 5'-CG-3' wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length or for any ISS comprising the sequence 5'-purine, purine, C, G, pyrimidine, pyrimidine, C, G-3'. The Examiner further asserts that "there is insufficient written description about the structure associated with function of all ISS." Office Action, page 7. In support of the rejection, the Examiner cites *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) and *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004) and states that "one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus." Office Action, page 8.

Applicants respectfully traverse these assertions and submit that other recent court decisions are more pertinent to the facts of the present invention than the cited decisions.

The written description requirement "may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure" and compliance with the requirement "is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" See *Amgen, Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.*, USPQ 65 USPQ2d 1385 (Fed. Cir. 2003); *Enzo Biochem, Inc. v Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002).

The claims are directed to conjugate molecules comprising a polynucleotide greater than 6 and less than about 200 nucleotides in length comprising an ISS, wherein the ISS comprises a CG dinucleotide.

Disclosed in the specification, and known in the art, are the structural characteristics of an oligonucleotide comprising an ISS required for a functional immunostimulatory oligonucleotide such that a skilled artisan would recognize possession of the claimed immunostimulatory oligonucleotides. See, for example, pages 36-37 of the specification. Applicants also note that Van Uden, cited by the Examiner, describes many CG-containing immunostimulatory oligonucleotides and, in turn, further cites a number of references describing additional CG-containing immunostimulatory oligonucleotides. The primary stated requirement for the immunostimulatory activity of the oligonucleotides in Van Uden is the presence of a CG dinucleotide. Thus, the connection between the 5'-CG-3' dinucleotide of the oligonucleotide and the immunostimulatory activity of the oligonucleotide was well known in the art at the time the instant application was filed.

Quoting from the Office's Written Description Requirement Guidelines, the court in *Enzo* stated that "the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... *i.e.*, complete or partial structure, other physical and/or chemical properties,

functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106 (emphasis added)." *Enzo Biochem, Inc. v Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002).

Applicants respectfully submit that the specification in combination with that known in the art provides a description of sufficient, relevant, identifying structural and functional characteristics of an ISS to adequately describe possession of the claimed genus to one skilled in the art.

Thus, the pending claims are fully described in the specification as filed. Accordingly, Applicants respectfully submit that the written description requirement has been met.

New Matter

Claims 75, 83, 84 and 86 were rejected for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

Although Applicants maintain that the previous claim 75 is described in the specification as filed for reasons of record, claim 75 has herein been amended in an attempt to respond to the concerns of the Examiner in order to facilitate disposition of this application.

Support for claim 75 is found at page 23, lines 14-15 of the specification. The specification describes a conjugate molecule in which the "ratio of (i) average mass of ISS-containing polynucleotide to (ii) average mass of antigen is (i) about or alternatively at least about 35, 40 or 45 to (ii) about 40." Thus, claim 75 is described in the specification as filed and does not contain new matter.

Accordingly, the pending claims are in compliance with the written description requirement.

In sum, Applicants submit that the pending claims fall within the subject matter that is enabled and described by the specification as filed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, second paragraph

Claims 71, 72, 83, and 84 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

Claims 63 and 75 recite that the ISS includes a CG dinucleotide. The claims use the conventional notation of "5'-cytosine, guanine-3' " to indicate the order of the cytosine and guanine relative to each other in the polynucleotide sequence.

The Examiner bases this rejection on the impression that "the amended claim 63 requires that the ISS comprises 5' cytosine (C)." Office Action, page 10. As apparent from the enablement rejection of the outstanding Office Action, the Examiner has understood the phrase "said ISS comprises 5'-cytosine, guanine-3'" to indicate that the ISS includes "additional undisclosed nucleotides at either or both ends so long the nucleotide sequence has a 5' cytosine and a 3' guanine." Office Action, page 4. This interpretation of this phrase in unfortunately incorrect and the ISS do not require a terminal 5' cytosine and a terminal 3' guanine.

As described in the specification and well known in the art, a CG (i.e., cytosine, guanine) dinucleotide is a necessary element of the claimed category of immunostimulatory sequences. The specification describes this, for example, on pages 36-37, in addition to listing over 75 examples of ISS for use in the invention. As can be seen, all of these ISS examples include at least one CG dinucleotide. Contrary to the Examiner's interpretation of the claim language, none of the examples have a C on the 5' end and a G on the 3' end.

As outlined herein, the ISS of the claimed invention comprises a CG dinucleotide. The references of Van Uden, Segal and Yamada cited by the Examiner also support Applicants' view of

the claim language, i.e., an ISS comprising a CG dinucleotide, as opposed to the Examiner's apparent view of a nucleotide sequence with a terminal 5' cytosine and a terminal 3' guanine.

In view of the proper interpretation of the pending claims, Applicants respectfully point out that the sequence recited in claims 71 and 83, i.e., 5'-purine, purine, C, G, pyrimidine, pyrimidine, C, G-3', includes the sequence recited in claim 63, i.e., 5'-CG-3', plus additional nucleotides. Since claims 63 and 75 use comprising language with the ISS sequence, dependent claims 71 and 83 have proper antecedent support in independent claims 63 and 75, respectively.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

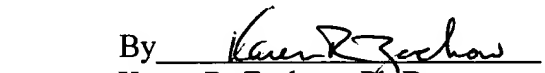
CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882001500.

Dated: August 20, 2004

Respectfully submitted,

By 
Karen R. Zachow, Ph.D.
Registration No.: 46,332

MORRISON & FOERSTER LLP
3811 Valley Centre Drive, Suite 500
San Diego, California 92130
Phone: (858) 720-5191
Fax: (838) 720-5125